FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

| ATTORNEY'S DOCKET NUMBER | U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR |
|---|---|
| 101195-39 | 09/743394 |

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/DE99/02181 | 12 July 1999 (12.07.99) | 10 July 1998 (10.07.98) |

TITLE OF INVENTION

**Method for Improvement of the Production of Adenovirus-based Vectors**

APPLICANT(S) FOR DO/EO/US

**Bernd Dorken; Gerhard Wolff; and Axel Schumacher**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

**Items 13 to 20 below concern document(s) or information included:**

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

| U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) | INTERNATIONAL APPLICATION NO. | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/743394 | PCT/DE99/02181 | 101195-39 |

21. The following fees are submitted:.

**BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :**

| | | CALCULATIONS PTO USE ONLY |
|---|---|---|
| ☐ | Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... **$970.00** | |
| ☒ | International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO ..... **$840.00** | |
| ☐ | International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **$690.00** | |
| ☐ | International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... **$670.00** | |
| ☐ | International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... **$96.00** | |

**ENTER APPROPRIATE BASIC FEE AMOUNT =** **$840.00**

Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)). **$130.00**

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | |
|---|---|---|---|---|
| Total claims | 7 - 20 = | 0 | x $18.00 | **$0.00** |
| Independent claims | 1 - 3 = | 0 | x $78.00 | **$0.00** |
| Multiple Dependent Claims **(check if applicable)**. | | | ☐ | **$0.00** |

**TOTAL OF ABOVE CALCULATIONS =** **$970.00**

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**. ☒ **$485.00**

**SUBTOTAL =** **$485.00**

Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). + **$0.00**

**TOTAL NATIONAL FEE =** **$485.00**

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐ **$0.00**

**TOTAL FEES ENCLOSED =** **$485.00**

| | |
|---|---|
| **Amount to be: refunded** | $ |
| **charged** | $ |

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **14-1263** in the amount of **$485.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **14-1263** A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

**The correspondence address associated with Customer No. 27387**

27387
PATENT TRADEMARK OFFICE

SIGNATURE

**Bruce S. Londa**
NAME

**33,531**
REGISTRATION NUMBER

**January 9, 2001**
DATE

526 Rec'd PCT/PTO 10 JAN 2001

| CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)<br>Applicant(s): **Bernd Dorken et al.** | | | Docket No.<br>**101195-39** |
|---|---|---|---|
| Serial No.<br>09/743394<br>**To be Assigned** | Filing Date<br>**To be Assigned** | Examiner<br>**To be Assigned** | Group Art Unit<br>**To be Assigned** |

Invention: **Method for Improvement of the Production of Adenovirus-based Vectors**

I hereby certify that the following correspondence:

**Patent application entering the national stage of PCT/DE99/02181 consisting of English translation of PCT application consisting of 7 pages of specification and 4 sheets of drawings; Prelimimary Amendment with marked-up sheets and clean copy of amended claims**

*(Identify type of correspondence)*

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

**January 10, 2001**
*(Date)*

**Kathleen D. Monical**
*(Typed or Printed Name of Person Mailing Correspondence)*

Kathleen D. Monical
*(Signature of Person Mailing Correspondence)*

EL 700070342 US
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P06A/REV02

PATENTS

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
Atty's Docket No. 101195-39

APPLICANT : Bernd Dörken et al.

FILED : Concurrently Herewith

FOR : Method for Improvement of the Production of Adenoviurs-based Vectors

PRELIMINARY AMENDMENT

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the application as follows:

**IN THE SPECIFICATION**

Please amend the specification as follows:

Page 1, line 2, please delete "Description" and insert --Background of the Invention--;

Page 2, before line 1, please insert --Summary of the Invention--;

Page 3, before line 15, please insert --Brief Description of the Drawings

Fig. 1A - Morphology of cultures of the Ad vector production cell line 293 infected with a mock infection;

Fig. 1B - Morphology of cultures of the Ad vector production cell line 293 infected with Ad vector Ad.CD (Cytosine deaminase);

Fig. 1C - Morphology of cultures of the Ad vector production cell line 293 infected with Ad vector Adlp21;

Fig. 1D - Morphology of cultures of the Ad vector production cell line 293 infected with Ad vector Adlp53;

Fig. 2 - Nutrient consumption as exemplified by the glucose concentration in the medium of cultures of the Ad vector production cell line 293 infected with different Ad vector (see Fig. 1);

Fig. 3 - Cell damage as exemplified by lactate dehydrogenase (LDH) concentrations in the medium of cultures of the Ad vector production cell line 293 infected with different Ad vector (see Fig. 1);

Fig 4 - Lactate concentrations in the medium of cultures of Ad vector production cell line 293 infected with different Ad

vector (see Fig. 1).

Description of the Preferred Embodiment--;

Page 4, lines 6-16, please delete these lines in their entirety.

**IN THE CLAIMS**

Please amend the claims in accordance with the marked-up copy and the clean copy attached hereto. Claims 2-6 have been amended and use claim 8 has been cancelled.

**REMARKS**

The above amendments were made to place the application into proper United States Patent Format.

Respectfully Submitted,

Bruce S. Londa
Attorney for Applicant
Norris, McLaughlin & Marcus P.A.
220 East 42nd Street, 30th Floor
New York, N.Y. 10017
Telephone: (212)808-0700
Telecopier: (212)808-0844

## Claims

**1.**

Method for the optimization of the production of Ad vector ~~characterized by the~~comprising the steps of transferring ~~of~~ the gene or the cDNA of p21 into a production cell line for Ad vector, and expressioning the gene or cDNA therein, irrespective of the endogenous state of the cell cycle regulator p21 in ~~those~~ the cell lines.

**2.**

The ~~M~~method of claim 1 ~~characterized by~~ comprising utilizing a constitutive promoter for the generation of stably transfected cell lines ~~utilizing a constitutive promoter~~.

**3.**

The ~~M~~method of claim 1 ~~characterized by~~comprising utilizing a regulatablve promoter for the generation of stably transfected cell lines ~~utilizing a regulatable promoter~~.

**4.**

The ~~M~~method of claim 1 ~~characterized by~~comprising utilizing a constitutive promoter for the generation of transiently transfected cell lines ~~utilizing a constitutive promoter~~.

**5.**

The ~~M~~method of claim 1 ~~characterized by~~comprising utilizing a regulatable promoter for the generation of transiently transfected cell lines ~~utilizing a regulatable promoter~~.

**6.**

The ~~M~~method of claim 1 ~~to 5 where~~wherein the transfer of the gene or the cDNA of p21 is carried out using known transfer techniques either as naked DNA or employing viral or nonviral vectors.

**7.**

The ~~M~~method of claim 1 ~~where~~ wherein the method is independent of the production cell line used.

~~8.~~

~~Use of the gene or the cDNA of the cell cycle regulator p21 in production cell lines for the production of adenoviral vector systems.~~

**Method for Improvement of the Production of Adenovirus-based Vectors**

**Description**

The invented method for improvement of the production of adenovirus-based vectors is characterized by gene transfer and overexpression of the cell cycle regulator $p21^{WAF1/CIP1}$ (p21), an inhibitor of cyclin-dependent kinases (CDK), in a production cell line.

As is well known, the methods in gene therapy are aimed at treating genetically based diseases by replacement of the defect genes by their intact wild type form. To do so, the wild type gene is transferred into the target tissue where this gene is normally expressed. For an effective therapy, the gene transfer has to reach a large proportion of the cells of the target tissue. With respect to efficacy, viral vectors to date are superior to nonviral vectors. The most commonly used viral vectors are adenovirus vectors (Ad vector).

The efficacy and quality of the amplification of adenovirus vectors in a production cell line critically depends on the time point when the cells are harvested. If the time point of cell harvest is to early then the yield of adenovirus-vector is to low, if the harvest is to late, the producing cells are already dead and, therefore, the adenovirus vector is lost. The latter is superimposed by the fact that amplification of the vector is accompanied by increased metabolic activity and nutrient consumption leading to acidification of the culture media which in turn is detrimental to the producing cells and, therefore, to the Ad vector.

Therefore, the underlying concept of the invention was to develop a method that can stop the progress of this harmful mechanism allowing the Ad vector producing cells to survive.

The task is completed by the transfer of the gene or the cDNA of p21 into a given cell line used for the production or Ad vector, irrespective of the endogenous status of p21 in that cell line. Overexpression of p21 prevents apoptosis of the cells after infection with the Ad vector to be amplified and improves culture medium conditions.

Employing known gene transfer techniques the gene or the cDNA of the cell cycle regulator p21 is introduced as an expression cassette either with or without a regulatable promoter into a cell line for the production of Ad vector.

P21 is a known cell cycle regulator which prevents re-entry of senescent cells into cell cycle progression by blockage of cyclin-dependent kinases. This function includes different mechanisms like hypophosphorylation of the protein product of the Retinoblastoma Gene (Rb), binding to proliferating cell nuclear antigen (PCNA), binding to CDK-cyclin complexes like cyclin D-CDK4, cyclin E-CDK2, and cyclin A-CDK2. Whereas the interaction between p21 and PCNA prevents DNA replication, the interaction of p21 with cyclin dependent kinase complexes results in arrest of the cell cycle in the $G_1$-phase. The presence of p21 and of its cellular function is of vital importance for the survival of a cell. This importance is, for instance, illustrated by the fact, that there exist almost no mutations that are able to survive.

As known, eukaryotic cells replicate their genome only during a defined and limited period of time which is termed as phase of DNA synthesis (S-Phase) of the cell cycle. The cell cycle comprises four phases: $G_1$-phase, S-Phase, $G_2$-phase and Mitosis. The duration of each phase is rather constant. The $G_1$-phase lasts in fast proliferating cells between 2 and 20 hours, S-

Phase between 6 and 10 hours, $G_2$-phase between 2 and 4 hours and Mitosis between 3 and 4 hours.

For the transfer of p21 into already known production cell lines conventional gene transfer methods are used to transfer either the naked DNA or DNA packaged into vectors which can be of viral or non-viral nature.

According to the invention one application is to stably transfer the gene or the cDNA of p21 in conjunction with either a constitutive promoter or a regulatable promoter.

Another application is to transiently transfer the gene or the cDNA of p21 in conjunction with either a constitutive promoter or a regulatable promoter.

With respect to the invention a stable transfer is defined as integration of the expression cassette for p21 into the genome of the target cell whereas after a transient transfer the expression cassette for p21 remains epichromosomal.

The method according to the invention provides the advantage that expression of p21 in the production cell prolongs survival which allows harvesting of the Ad vector at the optimal time point.

The invention will be explained with the example of the amplification of different Ad vectors in a production cell line.

Ad vectors are amplified in specific production cell lines. Irrespective of the cell type used and the **method for cultivation** expression of the vector encoded transgene occurs already during replication of the Ad vector. In case of the expression of a toxic gene, e.g. a proapoptotic gene, the production cells die earlier, expression of an antiapoptotic gene extends the survival of the cells. While in the first instance Ad vector production is impaired, the latter instance has a benefical effect on Ad vector production. Consequently, production cells used to amplify an Ad vector which carries the apoptosis-promoting gene p53 (Ad.p53) will enter

apoptosis much earlier than when used to amplify an Ad vector carrying an antiapoptotic gene like p21 (Ad.p21) (Fig. 1). This is demonstrated by the number of dead cells as well as the metabolic parameter of the culture whereby the latter determine the quality of the Ad vector yield. Therefore, medium conditions of cells producing Ad.p21 are significantly better than those of cells infected with Ad.p53 (Fig. 2 to Fig. 4)

**Figure Legends**

**Fig. 1** Morphology of cultures of the Ad vector production cell line 293 infected with different Ad vector. A: Mock infection, B: Ad.CD (Cytosine deaminase), C: Ad.p21, D: Ad.p53.

**Fig. 2** Nutrient consumption as exemplified by the glucose concentration in cultures of the Ad vector production cell line 293 infected with different Ad vector (see Fig. 1).

**Fig. 3** Cell damage as exemplified by lactate dehydrogenase (LDH) concentrations in the medium of cultures of the Ad vector production cell line 293 infected with different Ad vector (see Fig. 1).

**Fig. 4** Lactate concentrations in the medium of cultures of the Ad vector production cell line 293 infected with different Ad vector (see Fig. 1).

**Claims**

**1.**

Method for the optimization of the production of Ad vector characterized by the transfer of the gene or the cDNA of p21 into a production cell line for Ad vector and expression therein, irrespective of the endogenous state of the cell cycle regulator p21 in those cell lines.

**2.**

Method of claim 1characterized by the generation of stably transfected cell lines utilizing a constitutive promoter.

**3.**

Method of claim 1characterized by the generation of stably transfected cell lines utilizing a regulatable promoter.

**4.**

Method of claim 1characterized by the generation of transiently transfected cell lines utilizing a constitutive promoter.

**5.**

Method of claim 1characterized by the generation of transiently transfected cell lines utilizing a regulatable promoter.

**6.**

Method of claim 1 to 5 where the transfer of the gene or the cDNA of p21 is carried out using known transfer techniques either as naked DNA or employing viral or nonviral vectors.

**7.**

Method of claim 1 where the method is independent of the production cell line used.

**8.**

Use of the gene or the cDNA of the cell cycle regulator p21 in production cell lines for the production of adenoviral vector systems.

**Summary**

The invented method for improvement of the production of adenovirus-based vectors is characterized by gene transfer and overexpression of the cell cycle regulator $p21^{WAF1/CIP1}$ in a production cell line.

Claims

1.

Method for the optimization of the production of Ad vector comprising the steps of transferring the gene or the cDNA of p21 into a production cell line for Ad vector, and expressing the gene or cDNA therein, irrespective of the endogenous state of the cell cycle regulator p21 in the cell line.

2.

The method of claim 1 comprising utilizing a constitutive promoter for the generation of stably transfected cell lines.

3.

The method of claim 1 comprising utilizing a regulatablve promoter for the generation of stably transfected cell lines.

4.

The method of claim 1 comprising utilizing a constitutive promoter for the generation of transiently transfected cell lines.

5.

The method of claim 1 comprising utilizing a regulatable promoter for the generation of transiently transfected cell lines.

6.

The method of claim 1 wherein the transfer of the gene or the cDNA of p21 is carried out using known transfer techniques either as naked DNA or employing viral or nonviral vectors.

7.

The method of claim 1 wherein the method is independent of the production cell line used.

Abb. 1

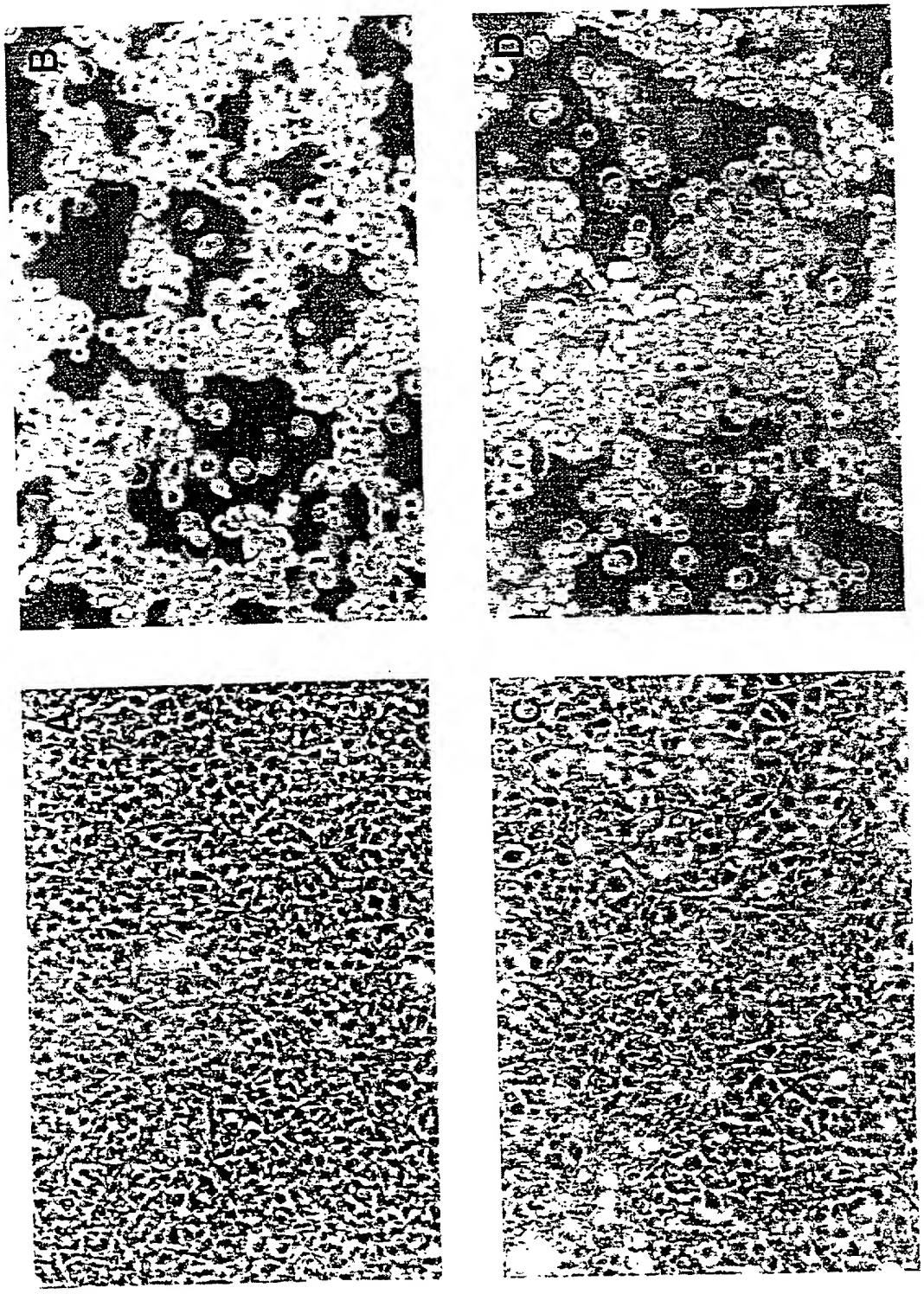



FIG. 1

Glucose

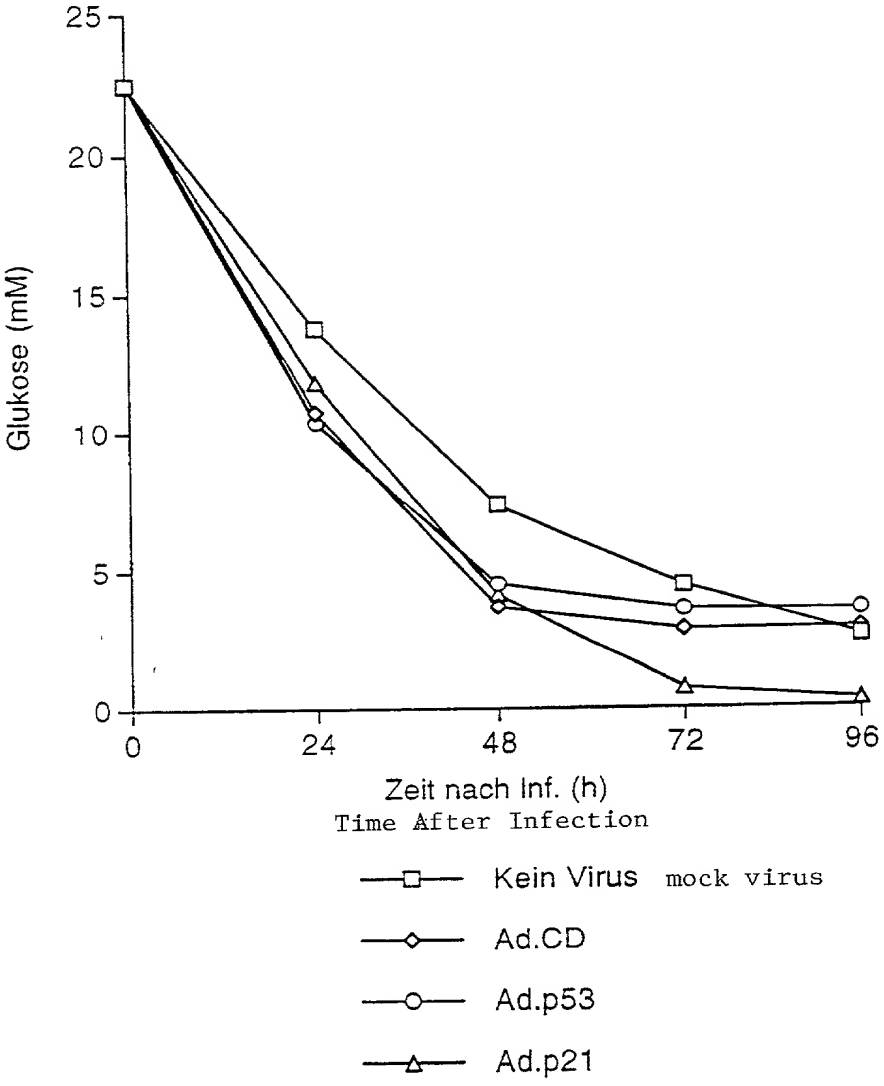



Fig. 2

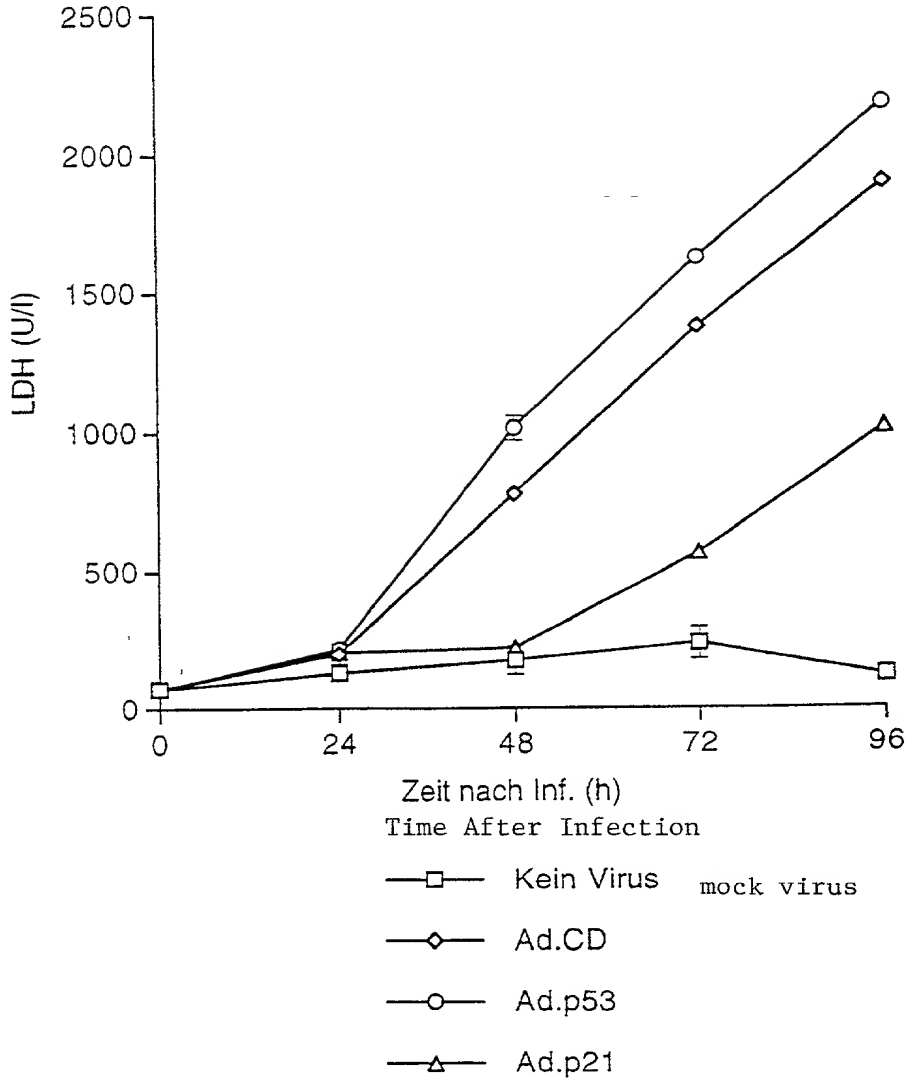
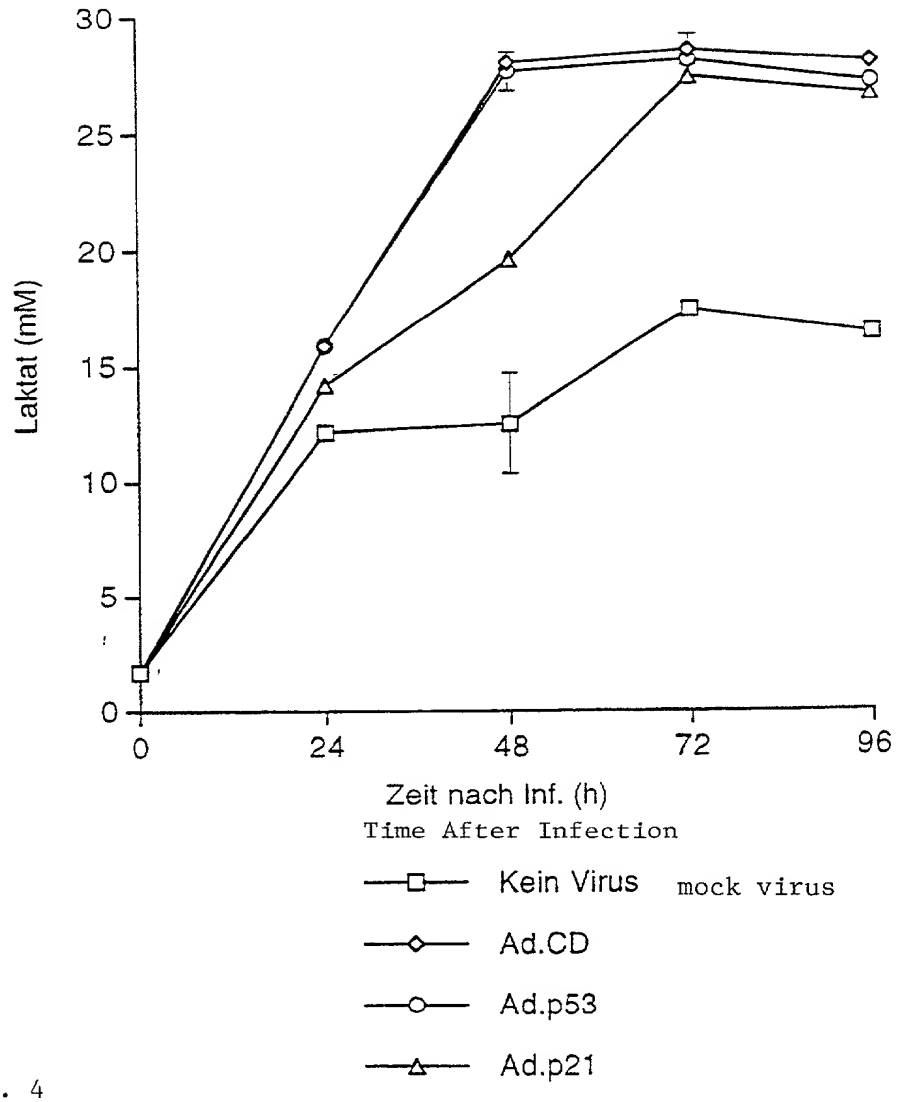

2500
2000
1500
1000
500
0
LDH (U/l)
0
24
48
72
96
Zeit nach Inf. (h)
Time After Infection
Kein Virus
mock virus
Ad.CD
Ad.p53
Ad.p21

Fig. 3




Lactate

Fig. 4

**Norris, McLaughlin & Marcus, P.A.**

220 East 42nd Street, 30th Floor
New York, NY 10017

If each inventor understands English, the Declaration and Power of Attorney below is suitable for use when filing a regular patent application and also when entering the national stage, in the case of an International application designating the USA under the PCT.

| COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION | Attorney Docket No. 101195-39 |
|---|---|

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name,
I believe I am the original, first and sole inventor (if only one name is listed below at 201) or an original, first and joint inventor (if plural names are listed below at 201-205) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method for Optimizing the Production of Adenovirus Vectors

the specification of which (check one)

____ is attached hereto

_✓___ was filed on _____12 July 1999_____

under Serial Number _PCT/DE99/02181__ and was amended on _____
(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I list below any prior foreign application(s) for patent or inventor's certificate in respect of which foreign priority benefits are claimed under 35 USC 119; and any prior foreign application(s) for patent or inventor's certificate in respect of which such foreign priority rights are not claimed and which has a filing date before that of any application in respect of which such foreign priority benefits are claimed:

| Application Number | Country | Filing Date (day, month, year) | Priority Claimed under 35 USC 119 |
|---|---|---|---|
| **198 30 907.4** | **Germany** | **10 July 1998** | YES: __✓_ NO: ____ |
| | | | YES:____ NO:____ |
| | | | YES:____ NO:____ |

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

| Application No. | Filing Date |
|---|---|
| | |
| | |
| | |

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

**Bruce S. Londa (33,531) Lorimer P. Brooks (15,155) William R. Robinson (27,224)
Kurt G. Brisco (33,141) William C. Gerstenzang (27,552) Robert A. Hyde (46,354)
Davy E. Zoneraich (37,267) Mark A. Montana (44,948) Stephen G. Ryan (39,015)
Victoria M. Malia (39,359)**

| | | | |
|---|---|---|---|
| **201** | Family Name<br>DÖRKEN | First Given Name<br>Bernd | Second Given Name |
| | City of Residence<br>Berlin | State or Foreign Country<br>Germany | Country of Citizenship<br>Germany |
| | Post Office Address<br>Lyckallee 47 | City<br>D-14055 Berlin | State & ZIP/Country<br>Germany |
| **202** | Family Name<br>WOLFF | First Given Name<br>Gerhard | Second Given Name |
| | City of Residence<br>Berlin | State or Foreign Country<br>Germany | Country of Citizenship<br>Germany |
| | Post Office Address<br>Gethsemanestrasse 5 | City<br>D-10437 Berlin | State & ZIP/Country<br>Germany |
| **203** | Family Name<br>SCHUMACHER | First Given Name<br>Axel | Second Given Name |
| | City of Residence<br>~~Berlin~~ | State or Foreign Country<br>Germany | Country of Citizenship<br>Germany |
| | Post Office Address<br>Charlottenstrasse 38 | City<br>D-13156 Berlin | State & ZIP/Country<br>Germany |
| **204** | Family Name | First Given Name | Second Given Name |
| | City of Residence | State or Foreign Country | Country of Citizenship |
| | Post Office Address | City | State & ZIP/Country |

| 205 | Family Name | First Given Name | Second Given Name |
|---|---|---|---|
| | City of Residence | State or Foreign Country | Country of Citizenship |
| | Post Office Address | City | State & ZIP/Country |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

| | |
|---|---|
| Signature of Inventor 201 Bernd Dahn | Date 01/11/01 |
| Signature of Inventor 202 | Date 01/08/01 |
| Signature of Inventor 203 | Date 01/08/01 |
| Signature of Inventor 204 | Date |
| Signature of Inventor 205 | Date |